REMARKS

Claims 1 – 8, 10, 12 – 16, 18 – 32 are currently pending. By this amendment, Claims 11 and 17 have been cancelled and the subject matter of these claims has been presented, in essence, in independent form, in new Claims 30 and 31. In addition, new Claim 32 presents the subject matter of both Claims 30 and 31, in essence, in independent form. Finally, Claim 27 has also been rewritten in independent form. Thus, the currently pending independent claims are Claims 1, 18, 27, and 30 – 32.

In the current Office Action, the Examiner withdrew the earlier prior art rejections based upon certain "collections" of the Bess, MacLaren, Ortyl, and Tanno references, and substituted in their place a new set of final prior art rejections based on a new "collections" of mostly new references. Claims 1 – 8, 10, 12 – 13, 16 and 18 – 29 were rejected as allegedly obvious over U.S. Patent No. 6,039,974 to MacLaren et al. ("MacLaren") in view of U.S. Patent No. 4,695,467 to Uemura et al. ("Uemura") and U.S. Patent No. 5,858,412 to Staniforth et al. ("Staniforth"). In addition, Claims 1 and 11 were rejected as allegedly obvious over a hypothetical combination of MacLaren, Uemura, and Staniforth, taken in further view of U.S. Patent No. 5,164,193 to Okada et al. ("Okada"). Finally Claims 1, 14, 15, and 17 were rejected as allegedly obvious over an imagined combination of MacLaren, Uemura, and Staniforth, taken in further view of U.S. Patent No. 6,713,089 to Bertelsen et al. ("Bertelsen").

Each of the foregoing rejections is respectfully traversed and favorable reconsideration is requested in view of the above amendments and following remarks.

I. Claims 1 and 18 Patentably Distinguish Over the Cited References.

Independent Claims 1 and 18 are directed to a bilayer tablet which includes, among other things, a first discrete portion which provides a sustained-release formulation of a sympathomimetic drug, such as pseudoephedrine, and a second discrete portion which provides an immediate-release formulation of a piperidinoalkanol, such as fexofenadine.

As amended herein, Claim 1 specifies that the first discrete portion of the tablet comprises, among other things, a cellulose binder selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, and mixtures thereof, wherein the hydroxypropyl cellulose has a molecular weight of at least 80,000, from about 5 wt. % to about 50 wt. % of ethylcellulose, and from about 2 wt. % to about 50 wt. % of a wax selected from

the group consisting of stearyl alcohol, cetyl alcohol. carnauba wax, white wax, yellow wax, microcrystalline wax. and mixtures thereof. Claim 18 already includes these plus other limitations.

Despite the Examiner's shift to an entirely new and different group of combinations of references. none of the presently cited references, either alone or in combination. can fairly be said to disclose or suggest a tablet composition of discrete bi-layers having the specified formulations of the claims for its parts.

As before, MacLaren is the only cited reference which is said to disclose any form of bilayer tablet. The Bertelsen reference discloses a single layer immediate release tablet. The Uemura. Staniforth. and Okada patents are all limited to single layer sustained release tablets.

Like before we have one "apple" reference and several "non-apple" references. Like before. they are not "obviously" combinable under a proper application of the law of obviousness so as to arrive at the subject matter of Applicants' claims.

The Examiner takes MacLaren as his starting point and primary reference. but he concedes that MacLaren fails to disclose or suggest a sustained release portion including (1) a cellulose binder selected from the group consisting of hydroxypropyl methylcellulose. hydroxypropyl cellulose. and mixtures thereof. wherein the hydroxypropyl cellulose has a molecular weight of at least 80,000, (2) ethylcellulose, and (3) from about 2 wt. % to about 50 wt. % of a wax selected from the group consisting of stearyl alcohol, cetyl alcohol. carnauba wax. white wax. yellow wax, microcrystalline wax, and mixtures thereof.

To overcome these deficiencies in the MacLaren reference. the Examiner turns to the Uemura and Staniforth patents. According to the Examiner. these two references would have led one of ordinary skill in the art to completely reformulate the sustained release portion of MacLaren's bilayer tablet. Specifically. the Examiner argues that Uemura would have led one of ordinary skill to modify MacLaren's sustained release portion by, among other things, (1) adding a first cellulose derivative binder such as hydroxypropyl methylcellulose and (2) materially reducing the amount of wax. At the same time. the Examiner asserts that Staniforth would have led one of ordinary skill to modify MacLaren's sustained release portion by adding a second cellulose derivative binder. namely ethylcellulose. This position is untenable.

Contrary to the Examiner's hypothesis, a person of ordinary skill in the art would not have used the Uemura and Staniforth references to "willy-nilly" reformulate the sustained

release portion of MacLaren's bilayer tablet to make it be what Applicants are claiming. Nothing in the cited art teaches doing this. It is difficult enough to formulate a single layer tablet which exhibits a desired set of strength. compression. and other physical properties, as well as a suitable rate of dissolution once taken by a patient. Staniforth, for instance, provides an extended discussion of these difficulties in the background of his patent.

These difficulties are amplified when one attempts to formulate a bilayer tablet including different active ingredient with different release profiles and compatibility issues. Each of the relatively thin layers of the bilayer tablet must separately be able to maintain its own physical ingretity and release its active component according to a desired release profile relative to the other part. And, at the same time, the two layers must adhere to each other to provide a single final tablet which remains aesthetically and functionally acceptable under the rigors of transport. storage, shelf-life. and other key factors. The background of the MacLaren reference provides an extensive list of failed attempts to formulate bilayer tablets which combine antihistamines with sympathomimetic drugs such as decongestants. These attempts are all said to have failed due to unacceptable chemical degradation of the active ingredients and /or because the final bilayer tablet exhibited unacceptable cracking and physical strength properties. These and other problems present challenges that belie any supposed hypothetical "mix and match" approach to selecting and combining bits. parts. and pieces of different references as if they were all smoothly interchangeable. If anything is obvious, it is that they are not interchangeable in the manner hypothesized by the Examiner.

Knowing these difficulties, one of ordinary skill in the art would not casually set about attempting to revise a bilayer tablet formulation. such as MacLaren's. which is already said to work satisfactorily for its intended purpose. One of ordinary skill would recognize that haphazard additions or other modifications or substitutions to the formulation will not predictably lead to a new formulation which exhibits acceptable compression and other physical properties while also providing the desired dissolution profile for each of the active ingredients.

Consequently, the Uemura reference would not have lead one of ordinary skill to just. materially reduce the amount of wax used in MacLaren. There is no reason in the art to do this. MacLaren specifically states that his goal is to provide a bilayer tablet form "of high integrity ... such that the tablet resists cracking on standing. has acceptable physical strength. and

provides acceptable content uniformity which meets USP requirements." (Col. 2, lines 20 – 26). In order to do accomplish this in a bilayer tablet, MacLaren instructs, not once but 3 times, that the extended release, decongestant portion of the bilayer tablet should include from 59 to about 81 weight percent carnauba wax. (Col. 2, lines 62 – 63; Col. 3, lines 28 – 29; Col. 12, lines 1 – 4) More preferably, the extended release, decongestant portion of the bilayer tablet should include from 66 to about 74 weight percent carnauba wax. (Col. 4, lines 10 – 11; Col. 12, lines 1 – 7). Thus, the mere fact that one example in Uemura happens to disclose a single layer tablet (for a vasodilator, not a sympathomimetic drug) having a relatively low amount of carnauba wax would have provided no incentive for a person of ordinary skill to use this composition in a bilayer tablet such as MacLaren's.

Much the same is true for the Examiner's further imaginings that the Uemura and Staniforth references would somehow have led one of ordinary skill to add not one but two different cellulose derivatives (hydroxypropyl methylcellulose from Uemera and ethylcellulose from Staniforth) to the MacLaren formulation for a bilayer tablet. Again, neither Uemura nor Staniforth disclose bilayer tablets, and neither reference would have lead one to make this wholesale substitution in MacLaren's carefully formulated bilayer tablet.

Even if, for the sake of argument, either Uemura or Staniforth might have led one of ordinary skill in the art to incorporate one cellulose derivative – either hydroxypropyl methylcellulose or ethylcellulose – (and there is no reason to suppose they would), the person of skill would still not have been led to incorporate both cellulose derivatives into the same formulation. In mentioning the possible use of hydroxypropyl methylcellulose or ethylcellulose, respectively, in a single layer tablet, Uemura and Staniforth disclose an "either, or" set of alternative excipients. At most one of ordinary skill hypothetically "might" have chosen to use one of these cellulose derivative binders disclosed in Uemura or Staniforth, but nothing in the references would have lead a person of ordinary skill to use both in combination. Although nothing suggests using even one of these in a bi-layer tablet formulation, using both at the same time is an even greater departure.

Finally, even if Uemura and Staniforth could somehow have led one to use both cellulose derivatives together, and they plainly would not, the Staniforth reference still would not have led one of ordinary skill in the art to use ethylcellulose in an amount from about 5 wt. % to about 50 wt. % of the sustained release portion of the bilayer tablet as called for in the

subject claims. While Staniforth makes a single, vague reference to the inclusion of ethycellulose in a single layer tablet (Col. 15, lines 54 – 58), Staniforth says nothing about the amount of ethylcellulose which should be used. Hence it fails to disclose or suggest this limitation of independent Claims 1 and 18.

For at least the foregoing reasons, independent Claims 1 and 18 (as well as their dependent claims) patentably distinguish over the purported combination of the MacLaren, Uemura, and Staniforth reference.

It is also noted that Claims 1 and 11 were rejected as allegedly obvious over the purported combination of MacLaren, Uemura, and Staniforth, taken in further view of Okada. However, Okada is only cited as allegedly disclosing the use of stearyl alcohol in sustained release formulation. While the use of stearyl alcohol in the sustained release portion of a bilayer tablet is permissible according to the "open" form of Claim 1, it is not required in Claim 1. Accordingly, Claim 1 (and its dependent claims) patentably distinguishes over the four-part collection of MacLaren, Uemura, Staniforth, and Okada for substantially the same reason it distinguishes over the three-part combination of MacLaren, Uemura, and Staniforth.

Finally, Claims 1, 14, 15, and 17 were rejected as allegedly obvious over the imagined combination of MacLaren, Uemura, and Staniforth, taken in further view of Bertelsen. However, Bertelsen is only said to disclose the use of certain low-substituted hydroxypropyl cellulose disintegrants in an immediate release formulation. While the use of certain low-substituted hydroxypropyl cellulose disintegrants in the immediate release portion of the bilayer tablet is permissible according to the "open" form of Claim 1, it is not required in Claim 1. Accordingly, Claim 1 (and its dependent claims) patentably distinguishes over the four-part collection of features fashioned from parts of MacLaren, Uemura, Staniforth, and Bertelsen for substantially the same reason it distinguishes over the three-part combination features from MacLaren, Uemura, and Staniforth.

II. Claim 27 Separately Distinguishes Over the Cited References.

Claim 27, newly rewritten in independent form, incorporates substantially all of the limitations of Claim 1 and, thus, distinguishes over the cited art for at least the reasons set forth above.

In addition, Claim 27 further specifies that the composition is essentially free of glidants such as silica, silicon dioxide, colloidal silicon dioxide, fumed silicon dioxide, magnesium trisilicate, powered cellulose, starch, talc, tribasic calcium phosphate, and the like. This provides an additional basis by which the subject matter of Claim 27 patentably distinguishes over the cited references. Among other things, they all use "glidants."

Claim 27 was alleged to be obvious over MacLaren taken in combination with Uemura and Staniforth; however, the primary reference, MacLaren, teaches that a bilayer tablet should include a "suitable glidant" such as silicon dioxide. *See* MacLaren, Col. 10, lines 15 – 17. MacLaren further directs at Col. 11, lines 16 – 44 that both parts of the bilayer tablet should include "glidants such as silicon dioxide, talc, and the like." These teachings resonate with those in Staniforth. Like MacLaren, Staniforth directs the use of a glidant material such as silicon dioxide in his composition. *See* Staniforth, Cols. 8 and 9.

Thus, if one of ordinary skill in the art were somehow motivated to make the hypothetical combination of MacLaren, Uemura, and Staniforth to produce a bilayer tablet (and there is no reason to suppose they would be), he or she would most certainly have included a glidant such as silicon dioxide in the tablet composition since both MacLaren and Staniforth teach that this is to be used and Uemura says nothing to contradict this directive. Accordingly, the purported combination of MacLaren, Uemura, and Staniforth would have lead one of ordinary skill away from the subject matter defined by Claim 27, rather than to it.

This provides a separate and independent basis by which Claim 27 patentably distinguishes from the cited prior art, over and above the reasons set forth above with respect to Claim 1.

III. Claims 30 – 32 Separately Distinguish Over the Cited References.

As noted above, new Claims 30 and 31 present the subject matter of former dependent Claims 11 and 17 in independent form. Further, new Claim 32 presents the combined subject matters of Claims 11 and 17 in single independent claim. While each of these claims includes all of the limitations of Claim 1 and thus distinguishes over the cited art for at least the reasons set forth above with respect to Claim 1, the further limitations of these claims provide additional reasons by which they patentably distinguish over the prior art.

Claim 11 was rejected as allegedly obvious over the four-part hypothetical combination of MacLaren, Uemura. Staniforth. and Okada. Okada is cited as teaching the use of stearyl alcohol, which the Examiner concedes is not mentioned in the MacLaren. Uemura, and Staniforth references. It is respectfully submitted, however, that the Okada reference could not have been "obviously" combined with the MacLaren, Uemura, and Staniforth to lead a person of ordinary skill to the subject matter of Claim 11 (and now Claim 30) as imagined by the Examiner.

Claim 30 specifically calls for a first discrete sustained release portion of the tablet which comprises. among other things, a mixture of: (i) lactose monohydrate; (ii) hydroxypropyl methylcellulose: (iii) from about 5 wt. % to about 50 wt. % of ethylcellulose; (iv) from about 2 wt. % to about 50 wt. % of stearyl alcohol: and (v) magnesium stearate. Notably, then. this sustained release formulation includes both hydrophobic materials, such as ethylcellulose and stearyl alcohol, and hydrophilic materials. such as lactose monohydrate. In contrast, Okada clearly segregates water insoluble materials into a first formulation, and water soluble materials into a second formulation. Thus, while Okada indicates that stearyl alcohol and ethycellulose may be combined into a first powder (Col. 3, lines 1 – 43), Okada instructs that any lactose or hydroxypropyl methylcellulose should be formulated separately (Col. 4, line 44 – Col. 5, line 3). This is a key distinction. In view of this, Okada could not have been "obviously" combined with MacLaren. Uemura, and Staniforth to provide a sustained release formulation according to Claim 30.

Turning next to former Claim 17 and to new Claim 31. Claim 17 was rejected as allegedly obvious over the four-part hypothetical combination of MacLaren, Uemura, Staniforth. and Bertelsen. The Examiner concedes that no combination of MacLaren, Uemura, and Staniforth teaches the inclusion of a low-substituted hydroxypropyl cellulose in the immediate release portion of a bilayer tablet. but contends that the Bertelsen patent fills in this gap. With all due respect, this is not a process like Tinker-Toys where parts of different reference would be isolated, out of context. and then somehow later fitted together in an attempt to make what Applicants are claiming. Nothing in the present case suggests constructing Applicants' claims from this or any other collection of references. The ACS Hospital case is still good law and a guiding principle as to when a combination of prior art teachings can properly be said to have been obvious under the law. It is respectfully submitted

that the Bertelsen reference, taken in combination with the MacLaren, Uemura, and Staniforth references, would not have lead a person of ordinary skill to the subject matter of Claim 17 (and now Claim 31) as proposed by the Examiner. This is simply not an "obvious" combination.

The focus of Bertelsen is to include alkalines in a pharmaceutical formulation for the purpose of pH control. With respect to low-substituted hydroxypropyl cellulose, Bertelsen says nothing beyond the fact that low-substituted hydroxypropyl cellulose may sometimes be of use as a pharmaceutical excipient. This hardly points to Applicants' claimed bi-layer construction. Bertelsen provides absolutely no reason to combine low-substituted hydroxypropyl cellulose with lactose and magnesium stearate as called for in Claim 31.

Finally, new Claim 32 combines the specific sustained release formulation of Claim 30 with the specific immediate release formulation of Claim 31. Thus, all of the foregoing arguments with respect to Claims 30 and 31 apply with equal force to Claim 32.

Importantly, moreover, the immediate release sustained release formulations specified in Claim 32 are found to be compatible with one another so as to facilitate final processing of the two layers into a stable, final tablet. For example, according to Claim 32, the sustained release portion includes lactose monohydrate while the immediate release portion includes lactose. The sustained release portion also includes hydroxypropyl methylcellulose while the immediate release portion includes a low-substituted hydroxypropyl cellulose. Further, both the sustained release portion and the immediate release portion include magnesium stearate. This synergistic matching of the components of the sustained release formulation with the components of the immediate release formulation is nowhere suggested in any of the cited references.

In light of the foregoing, the present amendment must, in all fairness, be acknowledged to place the application in a condition for allowance, and entry of the foregoing amendments and allowance of Claims 1 – 8, 10, 12 – 16, 18 – 32 is respectfully solicited.

In the event this response is not timely filed, Applicants hereby petition for the appropriate extension of time and request that the fee for the extension along with any other fees which may be due with respect to this paper be charged to our Deposit Account No. 12-2355.

Respectfully submitted,

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